Advanced Robotics and Automated Platforms for High-Throughput *In Vitro* ADME

Introduction: The Need for High-Throughput ADME

In vitro absorption, distribution, metabolism, and excretion (ADME) assessment is a foundational component of contemporary drug discovery, providing early and critical insight into the pharmacokinetic behaviour and developability of drug candidates. Comprehensive ADME profiling supports the early identification of liabilities associated with solubility, permeability, metabolic stability, clearance mechanisms, and drug–drug interaction potential. By enabling informed prioritisation and optimisation decisions, early ADME evaluation plays a central role in reducing late-stage attrition and improving overall resource efficiency.

The growing reliance on large, chemically diverse compound libraries—together with increasingly compressed discovery timelines—has markedly intensified the demand for rapid, reliable, and scalable ADME testing. High-quality ADME data generated early in discovery now directly inform medicinal chemistry strategies and guide structure–property relationship (SPR) and structure–pharmacokinetic relationship (SPKR) analyses. As a result, the ability to generate reproducible, data-rich ADME outputs at scale has become a critical determinant of programme success.

Despite its recognised importance, traditional ADME experimentation has historically been constrained by labour-intensive manual workflows, fragmented instrumentation, and limited standardisation across assay formats. These constraints typically restrict throughput to fewer than 100 compounds per day, introduce operator-dependent variability, and extend turnaround times, collectively delaying decision-making. As the number of parallel chemical series expands, manual and semi-automated approaches struggle to deliver the consistency, scalability, and data density required for modern discovery programmes.

Drawing on extensive experience across integrated drug discovery (IDD) programmes and large-scale compound screening, TCG Lifesciences highlights in this whitepaper how advanced robotics and automation are reshaping *in vitro* ADME experimentation. By integrating high-precision liquid handling, acoustic dispensing technologies, high-throughput analytical platforms, and intelligent data management systems, automated ADME workflows enable seamless, end-to-end execution and support rapid, data-driven decision-making across the discovery pipeline.

Robotic automation enables precise and reproducible execution of a broad spectrum of *in vitro* ADME assays, including aqueous and biorelevant solubility, parallel artificial membrane permeability assay (PAMPA), cell-based permeability models (Caco-2 and MDCK), plasma protein binding, metabolic stability in liver microsomes and hepatocytes, cytochrome P450 (CYP) inhibition and induction, and transporter interaction studies. Standardised control of liquid handling, incubation conditions, and timing is particularly critical for enzymatic and cell-based assays, where small variations can significantly influence outcomes.

Challenges in Traditional ADME Workflows

Conventional manual and semi-automated ADME workflows present several inherent limitations:

- Restricted throughput, limiting the number of compounds evaluated within a given timeframe
- Elevated experimental variability arising from pipetting inaccuracies and operator dependency
- Increased risk of error due to repetitive manual handling
- Limited scalability across assay formats, plate densities, and library sizes
- Fragmentation between experimental execution and downstream data analysis

Collectively, these challenges highlight the need for a paradigm shift towards fully integrated and automated ADME platforms capable of supporting modern drug discovery requirements.

Key Benefits of Robotics and Automation in ADME

Enhanced Throughput and Speed

Robotic platforms enable the parallel processing of hundreds to thousands of compounds across multiple ADME endpoints, substantially reducing assay turnaround times. Accelerated data generation shortens lead optimisation cycles and supports earlier, evidence-based go/no-go decisions.

Improved Reproducibility and Data Quality

Automation minimises operator-dependent variability by standardising critical aspects of assay execution, including liquid handling precision, reagent addition, and incubation timing. This level of reproducibility is essential for generating reliable datasets that enable meaningful cross-series and longitudinal comparisons.

Assay Miniaturisation and Cost Efficiency

Automated and acoustic dispensing technologies facilitate significant assay miniaturisation, reducing compound and reagent consumption while maintaining analytical sensitivity and robustness. This miniaturisation directly contributes to lower per-compound costs without compromising data quality.

Integrated Multi-Endpoint ADME Profiling

Fully automated workstations can be configured to execute multiple ADME assays in a coordinated manner, enabling comprehensive developability assessments from a single compound submission and streamlining downstream decision-making.

Data-Rich Outputs and Advanced Analytics

Integration with intelligent software platforms supports real-time data acquisition, automated quality control, and advanced analytics. These capabilities allow rapid identification of trends, outliers, and developability liabilities, strengthening SPR and SPKR analyses.

Scalability and Future Readiness

Robotic ADME platforms are inherently modular and scalable, allowing rapid expansion of throughput or assay panels to accommodate evolving project demands, emerging therapeutic modalities, and regulatory expectations.

Advanced Robotics and Automation: A Transformational Approach

TCG Lifesciences employs state-of-the-art robotic platforms to achieve end-to-end automation of *in vitro* ADME experimentation. These integrated systems combine:

- High-precision liquid handling and acoustic dispensing technologies
- Automated plate handling, scheduling, and workflow orchestration
- Seamless integration with LC–MS/MS systems, plate readers, and analytical instrumentation
- Real-time data capture, quality monitoring, and centralised analytics

Together, these capabilities establish a robust, scalable, and high-performance ADME ecosystem that enhances experimental consistency, maximises throughput, and delivers actionable insights across the drug discovery continuum.

Evolution of the *In Vitro* ADME Automation Platform

During the initial phase of laboratory establishment (2005–2007), *in vitro* ADME assays were primarily conducted using manual and electronic pipettes in tube-based or 96-well plate formats. Over time, the *in vitro* ADME team within the DMPK Services Department systematically expanded experimental capabilities and progressively increased automation to enhance operational efficiency and data quality.

The platform evolved from small, semi-automated systems to stand-alone automated liquid-handling workstations, and ultimately to high-throughput, fully integrated platforms. This progression enabled the transition of most ADME assays from 96-well to 384-well formats, substantially increasing throughput while preserving assay robustness.

The introduction of acoustic dispensing technology (Echo) enabled nanolitre-scale compound transfer, supporting enzymatic assays such as metabolic stability and CYP inhibition at reaction volumes of 5–10 µL. This miniaturisation resulted in up to a fivefold reduction in reagent and compound costs without compromising data integrity.

Parallel advances in bioanalytical automation, including the implementation of PAL3-RSI, HTX-PAL, and LS/HTS-PAL systems, further accelerated data generation by enabling ultrafast LC–MS/MS analyses with run times of less than 0.5 minutes per sample. Today, fully automated and integrated ADME workflows support scalable, high-quality data generation aligned with the demands of modern drug discovery.

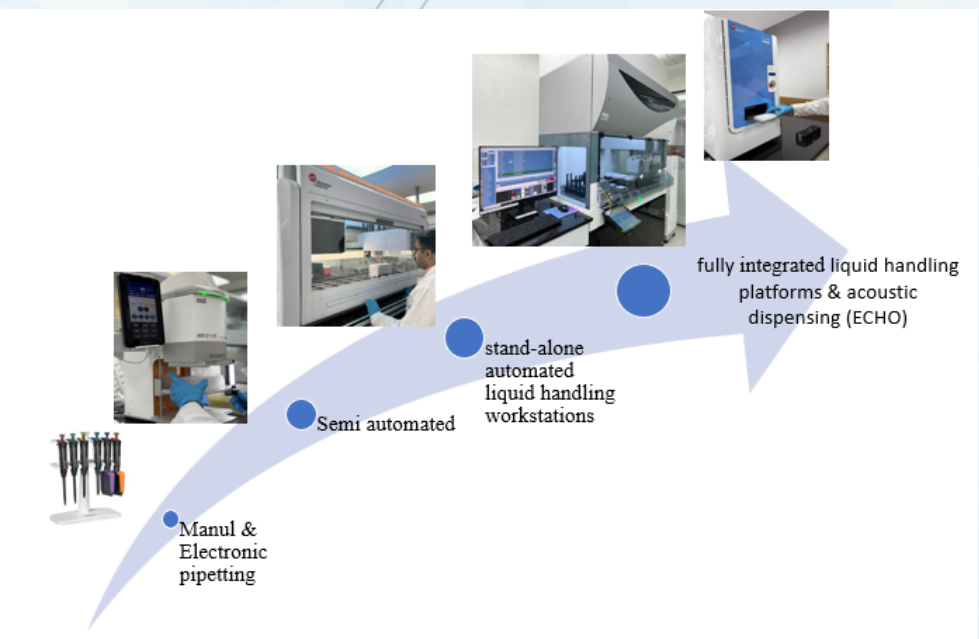

Figure 1. Upgradation of *In Vitro* ADME Automation Platform

Table-1: Comparison between manual and automated ADME workflows

Parameters	Manual workflow	Automated workflow
Throughput	30-50 compounds/ day	>500 compounds/ day
% CV	20-30 %	<5%
Turnaround	20 days	2 days
Cost/compound	$400-500	$100-200
Pipetting Precision (volume error)	±10%	±0.5%
Cross-contamination (false positives)	5-10%	<0.1%

Table-2: Representative Automated ADME Panel

Assay Category	Endpoints	Format	Throughput
Physicochemical	Kinetic/aqueous solubility, logD	384-well	5,000/week
Metabolism	HLM/Hep microsomes, hepatocytes	384-well	3,000/week
Protein Binding	Protein Binding	384-well	2,000/week
Drug Interactions	CYP IC50 (3A4/2D6/2C9), Induction	384-well	5,000/week
Transporters	P-gp, BCRP, OATPs, OCTs	96 -well	1,000/week
Permeability	PAMPA, Caco-2, MDCK-MDR1	96 -well	1,000/week

Automated *In Vitro* ADME Workflow

The fully automated *in vitro* ADME workflow implemented within the DMPK Services Department integrates compound transfer, assay execution, sample processing, and bioanalysis.

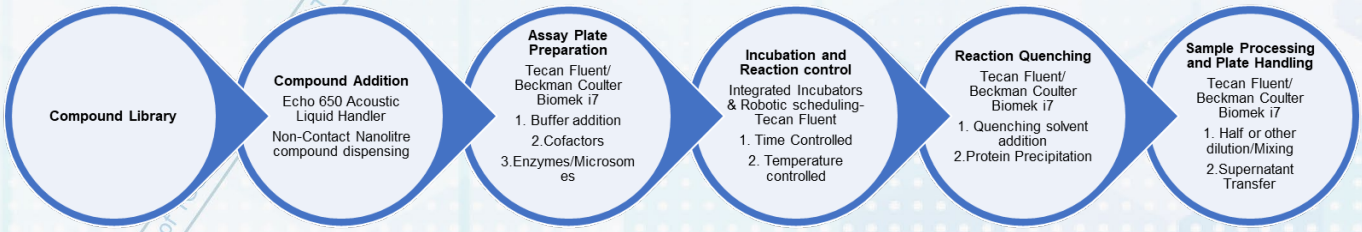

Figure 2. Automated *In Vitro* ADME Workflow

Compound dispensing is performed using the Echo 650 Acoustic Liquid Handler, enabling precise, contact-free nanolitre dispensing. Assay plate preparation, reagent addition, incubation, reaction quenching, and sample processing are executed on integrated liquid-handling platforms, including the Tecan Fluent and Beckman Coulter Biomek i7 workstations, with Apricot/INTEGRA systems supporting flexible and mid-throughput operations.

Automated plate handling and robotic scheduling ensure seamless workflow execution from assay setup through to LC–MS/MS sample preparation. Data capture, processing, and reporting are performed through integrated analytical and informatics systems, enabling reproducible, data-rich ADME profiling at scale.

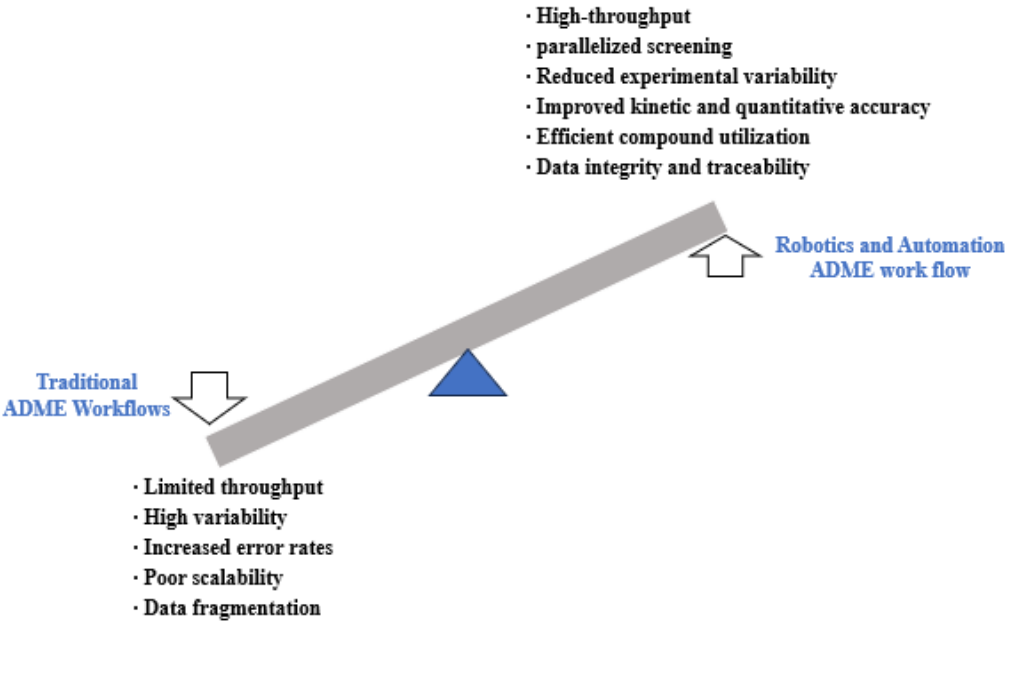

Figure 3. Traditional ADME workflow vs. Automated *In Vitro* ADME Workflow

Application of Robotic Platforms in ADME Screening

Robotic liquid-handling platforms play a central role in enabling high-throughput, reproducible, and scalable *in vitro* ADME screening. The coordinated application of complementary robotic systems allows efficient handling of diverse assay formats and throughput requirements while minimising manual intervention.

Echo 650 Acoustic Liquid Handler

The Echo 650 is primarily used for contact-free, nanolitre-scale compound dispensing from source to assay plates. This technology ensures high positional accuracy, reduces cross-contamination, and minimises DMSO carryover, making it well suited for early-stage screening of large compound libraries and dose–response studies. Acoustic dispensing supports 384- and 1536-well formats and reduces reagent costs by 70–90% without loss of sensitivity.

Figure 4. Echo 650 Acoustic Liquid Handler

Tecan Fluent Workstation

The Tecan Fluent platform serves as a fully integrated, high-throughput automation system for end-to-end ADME assay execution. Its modular deck design, robotic arm integration, and advanced scheduling software enable automated reagent dispensing, plate movement, incubation, reaction quenching, and sample processing for complex workflows such as metabolic stability, permeability, and transporter assays.

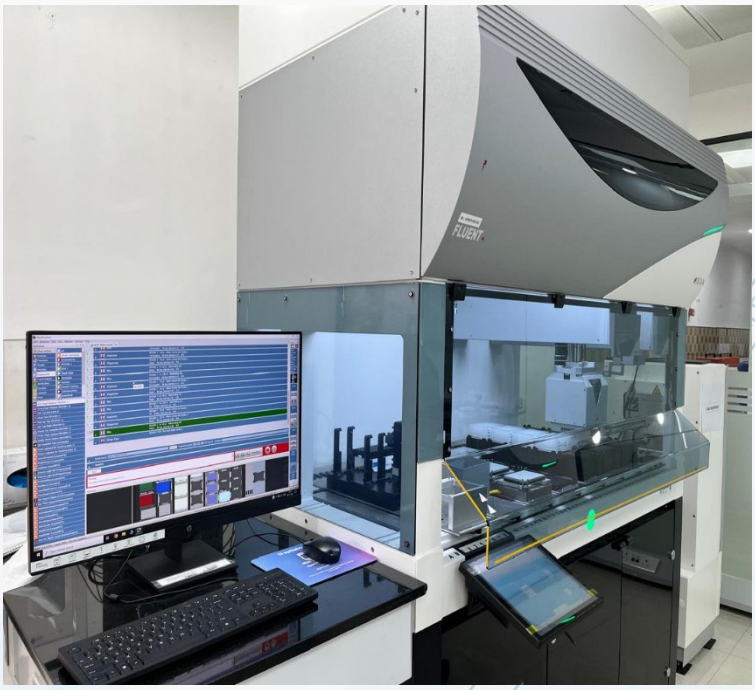

Figure 5. Tecan Fluent with incubator (fully integrated, high-throughput automation platform)

Beckman Coulter Biomek i7

The Biomek i7 system is employed for assays requiring high liquid-handling precision and flexible protocol design. Its accurate pipetting performance and customisable scripting support multi-step ADME assays, plate reformatting, sample clean-up, and bioanalytical transfer steps.

Figure 6. Beckman Coulter Biomek i7

Apricot and INTEGRA Systems

Apricot and INTEGRA liquid-handling platforms complement high-throughput systems by supporting mid-throughput assays and assay development activities. These platforms enable rapid protocol optimisation, method validation, and specialised ADME workflows where flexibility and quick turnaround are essential.

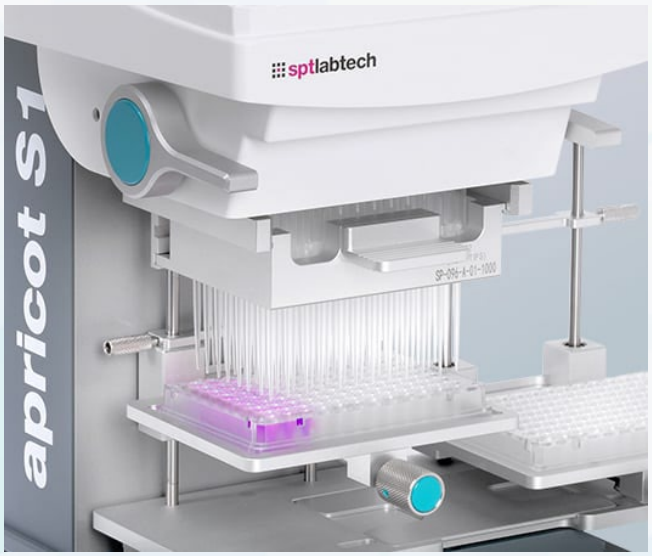

Figure 7. Apricot and INTEGRA ViaFlo-96/384

Table 3: The key feature of the available robotics at TCG and its application in ADME

Platform	Key Features	ADME Applications
Tecan Fluent	Microliter-nanoliter pipetting; flexible decks; automated incubation	Microsomal stability; plasma binding; solubility
Beckman Biomek i7	High-density processing; multi-assay scheduling	CYP assays; transporter studies (P-gp, BCRP)
Echo 650 Acoustic Handler	Contactless nanoliter dispensing; zero contamination	Dose-response; miniaturized screening as Metabolic stability / CYP inhibition assay
Apricot/INTEGRA	Modular customization; rapid protocol shifts	PAMPA permeability; bioanalysis prep, small scale ADME assay

Collectively, the coordinated use of these robotic platforms enables standardised, high-quality ADME data generation, improves throughput and reproducibility, and supports informed decision-making across integrated drug discovery programmes.

Conclusion

The scale and complexity of modern drug discovery demand ADME strategies that are both rapid and reliable. Robotic and automated *in vitro* ADME platforms address the limitations of traditional workflows by enabling high-throughput, standardised, and data-rich experimentation. Improved reproducibility and reduced turnaround times enhance the value of ADME data in guiding medicinal chemistry optimisation and early portfolio decisions.

Importantly, the adoption of robotics complements rather than replaces conventional laboratory tools. Manual, semi-automated, and fully automated workflows can coexist within a hybrid experimental ecosystem, maximising flexibility across different project phases and compound availability scenarios.

While significant progress has been made, challenges remain, particularly in adapting complex cell-based assays to high-density formats and standardising workflows across laboratories. Ongoing advances in automation, assay miniaturisation, and integrated analytics—together with continued standardisation efforts—are expected to further enhance the predictive power and translational relevance of early ADME profiling.